REMARKS

The specification is amended herein to recite a title that more accurately reflects the claimed invention.

Claims 24-43 are currently pending in the application.[1] Claim 24 is amended to recite that the placenta is drained of cord blood and flushed to remove residual blood. Support for the amendment to claim 24 is found in the specification at least at page 19, line 28 to page 20, line 27. Claim 24 is also amended to recite that the placental stem cells and placenta are human. Support for this amendment is found at least at pages 15-16. Claim 29 is amended to no longer recite "ABC-p". Claims 32-34 are amended to insert the word "that" between "placenta" and "has been perfused." Claims 41-43 have been amended to recite that the stem cells in the claimed compositions comprise $CD34^-$ stem cells. Support for these amendments is found in the specification at least at pages 4 and 28. Claims 44-50 are added. Support for these new claims is found in the specification at least at pages 3-15 and page 28, lines 13-27. No new matter is thus introduced by these amendments and new claims.

Attorney Docket Number

The Office Action cover sheet indicates that the Attorney Docket Number is 011307. Please amend the Attorney Docket Number for this application to **9516-101-999**.

The Claim Objections Should Be Withdrawn

The Examiner has objected to claims 31-34 "because a [conjunction] such as 'that' or 'which' should be inserted after 'a placenta'." Office Action at page 2. Applicant has so amended each of claims 32-34. Thus, the claim objection has been overcome. Claim 31 does not contain the phrase "a placenta," and has not been amended with respect to this objection.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

Claims 24-43 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Office Action at pages 2-4. In making the rejection, the Examiner contends that claim 24 is incomplete because while the "claims are directed to a method comprising seeding stem cells from a mammalian placenta . . . it is unclear how such stem cells are obtained." Office Action at page 2.

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[1] Applicant notes that the Office Action, under "Disposition of the Claims", states that claims 24-38 are pending, but the Examiner in the body of the Office Action correctly addresses claims 24-43.

"The test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" Manual of Patent Examining Procedure, § 2173.02, at 2100-214 (citation omitted). A claim is indefinite only when it "remains insolubly ambiguous without discernible meaning after all reasonable attempts at construction . . ." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings.*, 370 F.3d 1354, 1366 (Fed. Cir. 2004); *cert. denied*, 548 U.S. __, 2006 WL1788370, No. 04-1579 (June 30, 2006).

Applicant has amended claim 24 to clarify that the stem cells used in the claimed method of making tissue matrices, and in the claimed tissue matrices, are human placental stem cells. Human placental stem cells are described in the specification at least at page 28, lines 3-32, and methods of obtaining such cells are described in the specification at least at pages 15-28 and Examples 1 and 2. Human placental stem cells are not cord blood stem cells.

Moreover, and without conceding the propriety of the Examiner's rejection, Applicant has also amended claim 24, as suggested by the Examiner, to indicate how the placenta is treated. In particular, amended claim 24 is drawn to a method of seeding human placental stem cells onto a matrix, wherein the cells are from a human placenta that has been drained of cord blood and flushed to remove residual blood.[2] This amendment is made not to specify how the placental stem cells must be collected, but only to clarify that placental stem cells are obtained from the placenta, not from cord blood. Thus, claim 24, and claims depending from claim 24, are clear as to the types of cells to be used in producing the recited tissue matrix.

Because claim 24 as amended is definite, composition claims 41-43, which depend directly or indirectly from claim 24, are also definite. A person of skill in the art would understand, in light of the specification, that the claimed tissue matrix comprises human placental stem cells, not umbilical cord blood cells, and where to obtain human placental stem cells. Applicant respectfully requests that the Examiner withdraw the rejection of claims 24-43 on this basis.

Claims 24-43 are also rejected as indefinite apparently on the belief that, because the claims were directed to seeding "stem cells" onto a matrix, the term "stem cells"

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[2] On page 3 of the Office Action, the Examiner states that "residual cord blood could be present when the treatment [to remove cord blood from the placenta] is anything but perfusion for a lengthy period . . ." In fact, removal of cord blood can be accomplished by flushing the placenta with as little as 30-100 milliliters of perfusion solution. *See, e.g.*, page 21, lines 1-2 ("Generally from 30-100 ml (milliliter) of perfusion fluid is adequate to exsanguinate the placenta . . .").

encompasses any type of stem cell, and that the seeded stem cells "would be differentiated as soon as they are seeded . . . thus the metes and bounds of the end product tissue matrix are unclear." Office Action at pages 4-5. With respect, Applicant points out that the Examiner has not provided any support for this contention. As amended, claim 24 is sufficiently definite, as it requires only the seeding of human placental stem cells onto a matrix to form a tissue matrix. Once the seeding is complete, the method is completely performed; thus, there is no ambiguity with respect to the status or composition of the end product tissue matrix, as claimed in claims 41-43. Moreover, placental stem cells would not necessarily differentiate upon seeding onto a tissue matrix. As corroboration, the Declaration of Qian Ye, Ph.D. under 37 C.F.R. § 1.132 (the "Ye Declaration"), which is attached hereto as Exhibit 1, states that human placental stem cells are not expected to differentiate solely as a result of seeding onto a tissue matrix, *per se*. *See* Ye Declaration at paragraph 21.

A person of skill in the art would thus be able to readily discern what is claimed in amended claim 24, and claims depending from claim 24, when the claims are read in light of the specification. As such, the claims are not "insolubly ambiguous" and are therefore definite. Applicant respectfully requests that the Examiner withdraw this rejection of claim 24-43.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 24-43 are rejected under 35 U.S.C. § 112, first paragraph as nonenabled and lacking in written description support. Office Action at pages 4-6. The basis of this rejection appears to be doubt regarding whether certain stem cells recited in the pending claims exhibit surface marker characteristics as set forth in a subset of the claims. In addition, with respect to claim 30, the Examiner contends that "the majority of the recited markers belong to differentiated leukocytes, lymphocytes, or vascular cells, which are not stem cells." Office Action at page 6.

At the outset, and without conceding the propriety of the Examiner's contentions, but solely to further prosecution, Applicant has deleted recitation of "ABC-p" in the claims, rendering this basis for the rejection moot.

With respect to the remainder of the Examiner's contentions, as explained below, the Ye Declaration demonstrates that the markers referred to by the Examiner are all present in placental stem cells present in populations of cells collected by the methods taught in the specification. As such, the claimed methods and compositions are described and enabled in that the cells recited in the claims can routinely be produced.

As corroboration that the teaching provided in the '976 application teaches placental stem cells bearing markers described in the specification and recited in claims 29 and 30, the Ye Declaration describes fluorescence-activated cell sorting (FACS), RT-PCR, and other experiments that demonstrate that methods such as the perfusion methods described in the '976 application result in the collection of populations of cells that comprise human placental stem cells. *See* Ye Declaration, paragraphs 8-13. In particular, the Ye Declaration corroborates that these stem cells comprise $CD34^-$ stem cells. *See* Ye Declaration at paragraphs 14-16 and 18. The Ye Declaration also corroborates that these $CD34^-$ stem cells comprise cells that are also negative for SSEA3 and/or SSEA4, and/or positive for OCT-4 (Ye Declaration at paragraphs 14-17 and 19), and stem cells that are positive for CD10, CD29, CD44, CD54, CD90, SH2, SH3 and/or SH4, and/or negative for CD45 (Ye Declaration at paragraphs 14, 15 and 20). Thus, the '976 application describes the collection of cells that comprise stem cells that exhibit marker characteristics as recited in the pending method and composition claims. The '976 application therefore teaches and enables the methods of claims 24-40, and the compositions of claims 41-43.

Finally, with respect to the Examiner's comment that the specification states that "no attempts were made to further characterize these adherent cells," Office Action at page 5, Applicant respectfully points out that this phrase does *not* refer to stem cells, let alone placental stem cells. Rather, as the specification points out, this phrase refers to the "[s]pindle-shaped cells, round cells with large nuclei and numerous perinuclear vacuoles, and star-shaped cells with several projections" that were not characterized because "similar cells were observed in the culture of bone marrow, cord and peripheral blood, and [were] considered to be non-stem cell-like in nature." Page 43. Thus, the phrase quoted by the Examiner does not refer to placental stem cells, and is not relevant to the placental stem cells recited in the present claims.

Because, as set forth herein, the specification does, indeed, describe and enable the claimed methods for the production of a tissue matrix using the recited placental stem cells, Applicant respectfully requests that the Examiner withdraw this rejection of claims 24-43.

The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

The Examiner has rejected claims 24-27, 31, 35, 36, 41 and 42 under 35 U.S.C. 102(e) as allegedly anticipated by Pykett *et al.*, U.S. Patent No. 6,548,299 ("Pykett"). Office Action at pages 7-8.

For a reference to anticipate, the reference must disclose each and every limitation of the claim to which it is compared. *Schumer v. Laboratory Computer Sys., Inc.*, 308 F.3d

1304 (Fed. Cir. 2002); *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292 (Fed. Cir. 2002).

The Examiner states that amending claim 24 to include draining and flushing steps would obviate the rejection as to the method claims. Office Action at page 7. Without acquiescing to the propriety of the Examiner's contentions, and solely to facilitate prosecution, Applicant has so amended claim 24. Thus, Applicant respectfully requests that the Examiner withdraw this rejection of method claims 24-27, 31, 35 and 36.

With respect to composition claims, The Examiner states that Pykett discloses a three-dimensional matrix scaffold seeded with $CD34^+$ hematopoietic progenitor cells. Claims 41 and 42 have been clarified to specify that the placental stem cells comprise $CD34^-$ stem cells. Likewise, amended claim 43, and new claims 44 and 45 recite that the placental stem cells comprise $CD34^-$ stem cells, and new claims 46-50 recite that the placental stem cells are $CD34^-$ stem cells. These $CD34^-$ stem cells are not hematopoietic stem cells. *See* Ye Declaration at paragraph 13. As such, the claimed tissue matrices comprise different populations of stem cells than the tissue matrices disclosed by Pykett. Pykett, in fact, never teaches or suggests using non-hematopoietic stem cells, such as $CD34^-$ human placental stem cells. Pykett therefore does not anticipate claims 41 and 42. Applicant respectfully requests that the Examiner withdraw the rejection of claims 41 and 42 on this basis.

The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

The Examiner has rejected claims 24, 26-28, 35-40 and 43 as obvious over Pykett in view of Goldstein *et al.* (U.S. Patent No. 5,899,936; "Goldstein") and Atala (U.S. Patent No. 6,753,181; "Atala"). Office Action at pages 8-9. The Examiner cites Pykett for the disclosure that formed the basis of the 102(e) rejection, above. The Examiner cites Goldstein and Atala for teaching ratios of fibronectin to heparin for coating bioprostheses, and a process of decellularization of a natural tissue for making an implant. Office Action at page 8.

Obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art a reasonable expectation of success in practicing the claimed invention. The reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

With respect to method claims 24, 26-28 and 35-40, as noted above, Applicant has amended claim 24 to recite that the human placenta is drained of cord blood and flushed to remove residual blood. As noted above, this is an amendment the Examiner stated would overcome the 35 U.S.C. § 102 rejection of the method claims over Pykett because Pykett does not teach a method of seeding a tissue matrix with human placental stem cells. Neither Goldstein nor Atala supply the teaching or suggestion missing in Pykett, of seeding a tissue matrix with placental stem cells, let alone with placental stem cells from a placenta that has been drained and flushed to remove residual blood. The combination of Pykett, Goldstein and Atala, therefore, cannot teach a method of manufacturing a tissue matrix comprising placental stem cells, as claimed in claim 24 and method claims depending therefrom.

Likewise, with respect to composition claim 43, as explained above, Pykett does not teach a tissue matrix comprising $CD34^-$ placental stem cells because Pykett only teaches or suggests tissue matrices seeded with hematopoietic stem cells. Pykett never suggests the use of non-hematopoietic stem cells, such as placental $CD34^-$ placental stem cells. *See* Ye Declaration at paragraph 13. Neither Goldstein nor Atala supply the teaching or suggestion, missing in Pykett, of a tissue matrix seeded with placental stem cells that comprise $CD34^-$ stem cells. The combination of Pykett, Goldstein and Atala consequently does not teach or suggest the tissue matrix recited in claim 43, as amended.

Because the combination of Pykett, Goldstein and Atala fails to teach or suggest all limitations of the method or composition claims, the combination of references cannot render the claims obvious. Applicant therefore respectfully requests that the Examiner withdraw this rejection of the claims.

The Rejections Under 35 U.S.C. 102/103 Should Be Withdrawn

The Examiner has made several rejections of claims 41-43 under 35 U.S.C. 102 and 103. Applicant addresses each in turn, below.

The Rejection over Anderson and Thomas

The Examiner has rejected claims 41-43 under 35 U.S.C. 102(e) as anticipated by, or under 35 U.S.C. 103 as obvious over, Anderson *et al.* (U.S. Patent No. 6,328,762; "Anderson") as evidenced by Thomson *et al.*, *Science* 282:1145-1147 (1998)). Office Action at pages 9-10. The Examiner contends that Anderson teaches a tissue matrix (that is, a porous prosthetic implant) seeded with, *e.g.*, stem cells from bone marrow or embryonic stem cells. Office Action at page 9. The Examiner cites Thomson only as evidence that the recited markers were well-known in the art. Office Action at page 9.

Claims 41-43, as explained above, are drawn to tissue matrices that comprise human placental stem cells that comprise $CD34^-$ placental stem cells. Anderson does not teach a tissue matrix comprising any placental stem cells, let alone $CD34^-$ stem cells. As such, Anderson does not anticipate claims 41-43. Moreover, $CD34^-$ placental stem cells differ from other types of stem cells, such as the stem cells disclosed in Anderson. As corroboration, the Ye Declaration explains that the placental stem cells used in the present invention are different from bone marrow-derived stem cells, mesenchymal stem cells or embryonic stem cells. For example, whereas bone marrow-derived stem cells (*i.e.*, $CD34^+$ stem cells) can differentiate only into cells of hematopoietic lineages, the $CD34^-$ placental stem cells can differentiate into cells of at least three different non-hematopoietic lineages. *See* Ye Declaration at paragraphs 9-13. Moreover, the human $CD34^-$ placental stem cells comprise cells that are $SSEA3^-$ and $SSEA4^-$, whereas human embryonic stem cells are $SSEA3^+$ and $SSEA4^+$. *See* Ye Declaration at paragraph 19; *see also* Office Action, page 6, first paragraph. Moreover, $CD34^-$ placental stem cells form embryoid-like bodies in culture under proliferating conditions; mesenchymal stem cells (*e.g.*, mesenchymal stem cells from bone marrow) do not. *See* Ye Declaration at paragraph 22. Thus, the $CD34^-$ placental stem cells taught in the instant specification for use in tissue matrices differ from the stem cells taught by Anderson. As such, Anderson teaches a composition different than the claimed composition, and therefore does not anticipate claims 41-43.

With respect to the obviousness rejection, as explained above, Anderson fails to teach or suggest a tissue matrix comprising placental stem cells, which comprise $CD34^-$ stem cells.

Thomson does not remedy the deficiencies in the teachings of Anderson, because Thomson only discloses embryonic stem cells, which, as explained above, differ from the placental stem cells recited in claims 41-43. Given the above, a person of ordinary skill in the art, having in hand the teachings and suggestions of Anderson and Thomson, would have neither a suggestion of, nor a reasonable expectation of success in producing the tissue matrices of claims 41-43.

For the above reasons, Applicant respectfully requests that the Examiner withdraw this rejection of claims 41-43.

The Rejection Over Wu et al.

The Examiner has rejected claims 41-43 under 35 U.S.C. 102(e) as anticipated by, or under 35 U.S.C. 103 as obvious over, Wu *et al.* (U.S. Application Publication No. 2003/0109042; "Wu"), which purports to teach the construction of an "*ex vivo* immune system." The Examiner states that Wu teaches a three-dimensional culture of stem cells, *e.g.*, embryonic stem cells, comprising a three-dimensional support made of porous or fibrous

materials, and a method of using the culture for treating a patient or replacing tissue. Office Action at page 10, referencing the September 23, 2005 Office Action.

Wu does not anticipate the tissue matrices of claims 41-43. Claims 41-43, as explained above, are drawn to a tissue matrix comprising human placental stem cells, which comprise $CD34^-$ stem cells. Wu does not teach a tissue matrix comprising human placental stem cells of any kind. Moreover, Wu teaches only tissue matrices comprising hematopoietic stem cells. *See, e.g.*, paragraphs [0070]-[0073]. Though Wu teaches that embryonic stem cells are "hematopoietic" stem cells, the Ye Declaration explains that placental stem cells are different than embryonic stem cells. *See* Ye Declaration at paragraph 19. As explained above, human placental stem cells comprise $CD34^-$ stem cells, which are non-hematopoietic and are thus different from hematopoietic stem cells. *See* Ye Declaration at paragraph 13. Thus, the claimed tissue matrices differ from the tissue matrices taught by Wu. Because Wu does not teach tissue matrices comprising such placental stem cells, Wu cannot anticipate claims 41-43.

Moreover, the tissue matrices of claims 41-43 are not obvious over Wu. Wu does not teach or suggest tissue matrices comprising human placental stem cells that comprise $CD34^-$ stem cells. Moreover, as explained above, Wu, at best, teaches or suggests only tissue matrices comprising hematopoietic stem cells. While Wu refers to matrices that comprise embryonic stem cells, Wu characterizes such cells stem cells as hematopoietic. As such, Wu not only fails to teach all of the limitations of claims 41-43, but teaches away from the tissue matrices of claims 41-43, which comprise non-hematopoietic stem cells (*i.e.*, human $CD34^-$ placental stem cells). As such, a person of ordinary skill in the art, given only the teachings of Wu, would have neither a suggestion nor a reasonable expectation of success in producing the tissue matrices of claims 41-43. Thus, Wu cannot render the tissue matrices of claims 41-43 obvious.

For the above reasons, Applicant respectfully requests that the Examiner withdraw this rejection of claims 41-43.

The Rejection Over Buttery et al.

The Examiner has rejected claims 41-43 under 35 U.S.C. 102(a) as anticipated by, or under 35 U.S.C. 103 as obvious over, Buttery *et al.*, *Tissue Eng.* 7:89-99 (2001) ("Buttery"). Office Action at pages 12-13, referencing the September 23, 2005 Office Action. The Examiner states that Buttery teaches a culture of embryonic stem cells on a feeder layer and a matrix comprising fetal osteoblasts and collagens seeded with embryonic stem cells.

Buttery does not anticipate the tissue matrices of claims 41-43. Claims 41-43, as explained above, are drawn to tissue matrices comprising human placental stem cells that

comprise $CD34^-$ stem cells. Buttery does not teach matrices comprising human placental stem cells. Moreover, $CD34^-$ placental stem cells are different from embryonic stem cells. *See* Ye Declaration at paragraph 19. Thus, the tissue matrices ostensibly taught by Buttery differ from the claimed tissue matrices, and, therefore, Buttery does not anticipate claims 41-43.

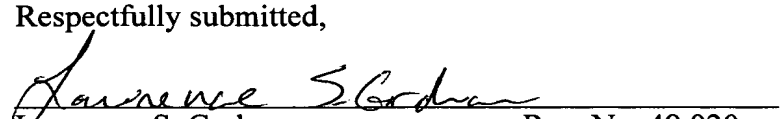
Moreover, Buttery does not render the tissue matrices of claims 41-43 obvious. Buttery does not teach or suggest a tissue matrix comprising human placental stem cells. Indeed, Buttery fails to teach how such cells may be obtained or cultured, because Buttery only teaches the culture of embryonic stem cells. As such, Buttery fails to teach or suggest all limitations of claims 41-43. Thus, a person of ordinary skill in the art, given only the teachings of Buttery would have had neither a suggestion nor a reasonable expectation of success in producing the tissue matrices of claims 41-43. As such, Buttery cannot render the tissue matrices of claims 41-43 obvious.

For the above reasons, Applicant respectfully requests that the Examiner withdraw this rejection of claims 41-43.

CONCLUSION

Applicant respectfully requests that the above remarks and accompanying documents be entered in the present application file. An early allowance of the present application is respectfully requested. No fee, other than an extension-of-time fee, is believed due for this Amendment. However, if any fee is deemed to be due, please charge such fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,



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